categories: genes with relative fold-change of mRNA less than 10 fold (A), genes with relative fold-change of mRNA between 10 and 100 fold (B), genes with relative fold-change of mRNA more than 100 fold (C).

Conclusions: These results indicated that resistin, the adipocyte-derived cytokine, could be an important link between obesity and osteoarthritic (OA) joint disease. Resistin is a proinflammatory and destructive mediator of joint inflammation in human joint, and might be considered as a potential therapeutical target in joint degenerative diseases such as OA.

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PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORα AGONISTS DECREASE INFLAMMATORY AND DESTRUCTIVE RESPONSES OF OSTEOARTHRITIC SYNOVIUM, CARTILAGE AND HOFFA'S FAT PAD

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Purpose: Although osteoarthritis (OA) was originally described as a noninflammatory arthropathy, inflammatory responses in synovium and cartilage may contribute to disease progression. Inflammation is caused by direct biomechanical perturbation or reaction to cartilage matrix degradation. Recent evidence has emerged for a role of the Hoffa's fat pad in the development and progression of OA by the secretion of pro-inflammatory cytokines. The Hoffa's fat pad is located in the knee, intraarticular and extrasynovial, under the patella.

Peroxisome Proliferator-Activated Receptorα (PPARα) is a member of class I nuclear receptor superfamily of ligand-dependent transcription factors. Anti-inflammatory effects of PPARα agonists have been described in adipose tissue, liver, blood vessels, kidney, macrophages and mesangial cells. We hypothesized that addition of synthetic PPARα agonist Wy-14643 exerts anti-inflammatory effects in OA joint tissues.

Methods: Explants of synovium (n=9), cartilage (n=9) and Hoffa's fat pad (n=10) were obtained from OA patients that underwent total knee arthroplasty. Explants were cultured in DMEM-high glucose with ITS, with(out) 100 μM PPARα agonist. 10 ng/ml Il-1β was added as a pro-inflammatory stimulus. Gene expression analysis was performed on cartilage explants (MMP1, MMP3, MMP13, aggrecan, collagen type II) and on synovium explants (MMP1, MMP3, MMP13, Il-1β). The culture supernatant of cartilage and synovium samples was analysed for NO production. Supernatant of cartilage was analysed for GAG release. The culture supernatant of Hoffa's fat pad was analysed with ELISA for leptin, adiponectin, resistin, MCP-1, TNFα, Il-1β, Il-6, Il-4 and Il-10. A decrease or increase was defined as more than 25 % of the control value. Results were analysed with non-parametric tests.

Results: Addition of PPARα agonist decreased mRNA expression of cartilage with 76 % for MMP1 (p=0.12), 68 % for MMP3 (p=0.02) and 87 % for MMP13 (p=0.01). Addition of IL-1β decreased collagen type II gene expression a 15-fold. Addition of the PPARα agonist decreased this expression even more with 49% (p=0.02). Aggrecan mRNA expression was not influenced by the PPARα agonist. NO production of cartilage showed a trend towards a decrease by the addition of PPARα agonist. The release of GAG in cartilage culture supernatant was lower after addition of 100 μM PPARα agonist (p=0.06).

A trend towards decrease could be observed for MMP1, MMP3 and MMP13 after adding PPARα agonist. Il-1β mRNA expression and NO production by synovium was not influenced by the PPARα agonist.

In culture supernatant of Hoffa's fat pad, MCP-1 (p=0.01), Il-4 (p=0.03) and Il-10 (p=0.03) were decreased after adding PPARα agonist. 7 donors showed a decrease and 2 an increase for TNFα production (p=0.18). Leptin, resistin and Il-1β showed a trend towards more donors with a decrease. Adiponectin and Il-6 were not influenced.

Conclusions: Addition of 100 μM PPAR α agonist Wy-14643 decreased IL-1β induced MMP gene expression, NO production and GAG release in cartilage and had an effect on collagen type II, but not on aggrecan production. A non significant decrease was seen for MMP expression in synovium. The production of pro- and anti-inflammatory cytokines by Hoffa's fat pad was decreased by adding 100 μM PPAR α agonist. In general, the use of PPAR α agonist Wy-14643 showed promising results in inhibiting inflammatory processes in OA joint tissues. The use of these synthetic ligands for treatment of OA should be further explored.

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OSTEOARTHRITIS SUSCEPTIBILITY GENES ARE ASSOCIATED WITH VARIATIONS IN HIP MORPHOLOGY

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Purpose: It has been suggested that many cases of primary hip OA are actually caused by mild morphological variations in the shape of the hip. Interestingly, genes that have been found to affect susceptibility for OA such as FRZB, GDF5 and DIO2, are involved in endochondral ossification and regulate the process of skeletal formation.

In this study, we have quantified the shape of the hip in sibling pairs of the GARP study, who have symptomatic OA at multiple joint locations. We estimated familial aggregation of hip shape and investigated whether shape is affected by the genetic variation at the OA susceptibility genes.

Methods: A Statistical Shape Model was created of the shape of the proximal femur and pelvis of radiographs of the hips of sibling pairs of the GARP study. The method results in a set of independent modes that together quantitatively describe the total shape, while each mode separately describes a specific characteristic of the shape. This preliminary data concerns 74 sibling pairs (148 subjects), of which 29 subjects had radiographic signs of hip OA (KL>1). Familial aggregation (heritability) of shape was estimated from the variance within and between siblings. Associations between shape and SNPs of the FRZB, GDF5 and DIO2 genes were tested using mixed model regression with height, gender, age, BMI, and OA status (KL>1 for 0, 1 or 2 hips) as co-variables. In these analyses we modeled familial and left and right hip dependencies through random effect variables.

Results: 5 out of 30 modes showed significant familial aggregation describing over 60% of the total variation in shape. OA status associated significantly with femurs with a stocky appearance (mode 6, p=0.03), a short superior neck (mode 11, p=0.002) and a small offset between superior neck and head (mode 17, p=0.035). It is unclear whether these associations are the result of the OA disease process or point to a factor underlying the OA process. Modes 5 (p=0.012) and 16 (p=0.004) showed a dose response association with respectively DIO2 OA susceptibility SNPs rs225014 and rs12885300. Both modes are descriptors of acetabular shape. Mode 3 associated significantly (p=0.002) with the FRZB SNP rs388326 and describes the slenderness of femur and pelvis (see Figure 1 for modes 3 and 5). No associations were found for GDF5.

Conclusions: These initial analyses showed that a large part of the variation in hip shape is attributable to familial aggregation (>60%) which reflects both shared genetic and environmental